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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,175	03/01/2002	Bryon E. Petersen	A32212-PCT USA	1973

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BAKER & BOTTS
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,175	PETERSEN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending in the present application.

This application contains claims 1-14 and 20-24 drawn to an invention nonelected in Paper No. 11/10/03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 15-19 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the previous Office Action mailed on 2/25/04 (pages 2-8).

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 8/30/04 (pages 4-8) have been fully considered, but they are not found persuasive.

1. Applicants argue that the instant specification teaches that the bone marrow cells can be obtained by standard bone marrow aspiration techniques known in the art, and bone marrow cells can be enriched for stem cells, stimulated either *in vitro* prior to administration to a patient or *in vivo* after administration to a patient for proliferation and/or differentiation. Therefore, on the basis of the instant disclosure one of ordinary skill in the art would be able to practice the presently claimed invention without undue experimentation. Additionally, using the teachings of the present application Applicants are able to obtain pancreatic-like cells from bone marrow cells, and upon implanting these cells under the kidney capsule of chemically-induced diabetic mice, complete normalization of blood glucose levels and long-term survival are obtained as evidenced by the post-filing article of Oh et al. (Laboratory Investigation 84:607-617, 2004). Applicants argue that this study indicates that bone marrow cells can in fact serve as a source for the production of a sufficient number of pancreatic cells to exert a therapeutic effect in recipients into which the cells are implanted, and that similar exposure of the pancreatic DPPIV-positive cells of the instant invention to high glucose *in vivo* would lead to a similar amount of proliferation and differentiation of the bone marrow cells as observed *in vitro* in the study of Oh et al.

Please note that the post-filing art of Oh et al. teaches that bone-marrow cells are induced to differentiate into insulin-producing cells **under specific defined *in vitro* conditions** (e.g., BM cells are cultured on 0.3% rat tail collagen in the presence of 1% DMSO in serum-free for 3 days, maintained for an additional 7 days in a DMSO-free DMEM medium containing 10% FBS with either a low (5.5 mM) or high (25 mM)

concentration of glucose, with cells cultured under high-glucose conditions form small spheroid clusters resembling "islet-like" clusters), and that subcapsular renal transplantation of these cell aggregates, **not bone marrow cells as claimed**, into streptozotocin-induced hyperglycemic NOD/scid mice results in lowered circulating blood glucose levels and maintenance of normal glucose levels for up to 90 days post-transplantation. The present application not only fails to teach the specific cultured conditions used in the post-filing art of Oh et al. to differentiate bone marrow cells into "pancreatic-like" cells, but the instant claims are drawn to a method for stimulating pancreatic regeneration in a subject having a pancreatic disorder comprising administering of bone marrow cells, and not "pancreatic-like" cell aggregates induced under specific cultured conditions, into said subject to attain therapeutic effects contemplated by Applicants. Accordingly, the positive effects that are obtained under the method taught by Oh et al are not reasonably extrapolated to the therapeutic effects contemplated by Applicants for the presently claimed invention. Moreover, Oh et al. teach specifically that a renal subcapsular transplant of non-cultured BM cells (10 millions, see page 609, col. 2, bottom of third paragraph) did not result in either a lowered circulating blood glucose levels nor a maintenance of normal glucose levels for any period of time (see Figure 7).

Accordingly, in light of the Wands factor analysis set forth in details in the previous Office Action, and coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and/or use the presently claimed invention.

2. With respect to the issues of introducing antigenically mismatched cells or tissues, Applicants contend that the scientific literature at the time of filing of the present application was replete with examples demonstrating the efficacy of adjunct immunomodulatory treatments in reducing or abrogating strong adverve immune response against the transplanted cells or tissues as evidenced by the teachings of Liu et al. (Transplantation proceedings 31:625-626, February-March 1999) and Namii et al (Transplantation proceedings 29:1738-1739, 1997). Therefore, Applicants assert that a skilled artisan would be able to practice the instant invention without undue experimentation based on the teachings of the present application.

It is noted that none of the teachings of Liu et al or Namii et al relates to the administration of any bone marrow cells into a subject having a pancreatic disorder. Additionally, both teachings showed an improvement of organ allografts, and not any grafts including xenografts, expressing CTLA4-Ig. Moreover, there is no evidence of record indicating that even bone marrow cells transformed or transfected with an adenoviral vector containing the CTLA4-Ig gene are capable to differentiate and/or proliferate into pancreatic cells in a sufficient number in a subject having a pancreatic disorder to yield the therapeutic effects contemplated by Applicants, particularly in light of the results reported by Oh et al. which showed that a renal subcapsular transplant of non-cultured bone marrow cells in streptozotocin-induced hyperglycemic NOD/scid mice (10 millions, see page 609, col. 2, bottom of third paragraph) did not result in either a lowered circulating blood glucose levels nor a maintenance of normal glucose levels for any period of time (see Figure 7).

3. With respect to the issue of any route of delivery, Applicants argue that engraftment of bone marrow cells into the pancreas could be achieved by several different routes, and in light of the amendment of claims 16 and 19, the specification is enabled for the presently claimed invention.

It is noted that claim 15 still encompasses any route of delivery at any site in a subject having a pancreatic disorder. Nevertheless, the route of administration is only one of several issues being raised for the non-enablement of the presently claimed invention (see responses to Applicants' arguments in the preceding paragraphs 1-2).

4. With respect to claim 18, Applicants argue that many examples of a successful application of gene transfer, either *ex vivo* or *in vivo*, could be found in the scientific literature at the time of filing of the present application. For example, Liu et al. demonstrated that local production of CTLA-4Ig by adenoviral-mediated gene transfer to the pancreas induces permanent allograft survival and donor-specific tolerance; and Namii et al. showed that adenoviral vector containing the CTLA4-Ig gene improves transgene expression and graft survival. Accordingly, Applicants contend that claim 18 is enabled based on the teachings of the instant application in combination with the knowledge provided by the prior art.

As noted previously, none of the teachings of Liu et al or Namii et al relates to the administration of any bone marrow cells into a subject having a pancreatic disorder, nor is there any evidence of record indicating or suggesting bone marrow cells transformed or transfected with an adenoviral vector containing the CTLA4-Ig gene or any other genes are capable to differentiate and/or proliferate into pancreatic cells in a sufficient

number in a subject having a pancreatic disorder to yield the therapeutic effects contemplated by Applicants.

Once again, in light of the Wands factor analysis set forth in details in the previous Office Action, and coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and/or use the presently claimed invention.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER